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PERCUTANEOUS TOXICOKINETICS OF HYDRAZINE AND H-70 IN THE RABBIT

WILLIAM C. KELLER
JAMES P. F. MURPHY
MELVIN E. ANDERSEN
KENNETH C. BACK

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AIR FORCE AEROSPACE MEDICAL RESEARCH LABORATORY
AEROSPACE MEDICAL DIVISION
AIR FORCE SYSTEMS COMMAND
WRIGHT-PATTERSON AIR FORCE BASE, OHIO 45433

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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals, "Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

ANTHONY A. THOMAS, MD
Director
Toxic Hazards Division
Air Force Aerospace Medical Research Laboratory

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The percutaneous absorption of anhydrous hydrazine and H70 (70% hydrazine) has been studied. The half life of hydrazine in the rabbit was determined to be 2.3 hours. The absorption half life for both anhydrous hydrazine and H70 was estimated to be 10-20 minutes. Anhydrous hydrazine was absorbed to a greater extent (86%) than hydrazine as H70 (55%). The extent of percutaneous absorption in the rabbit appears to be greater than that in the dog.

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PREFACE

This research was performed in the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory from July 1979 through September 1980. It was performed in support of Project 6302, "Occupational and Environmental Toxic Hazards in Air Force Operations;" Task 630201 "Toxicology of Conventional Propellants, Industrial Chemicals and Materials;" Work Unit 63020104, "Toxicology and Pathology of Chemicals and Materials used in Air Force Operations."

The authors acknowledge the technical assistance of SSgt James Kroon, A1C Whittaker, and Mr. Kenneth Beers.

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INTRODUCTION

Hydrazine (H_2NNH_2), a polar, water-miscible base, is a versatile reducing agent with wide application in a variety of industrial processes. It is used as a polymerization catalyst, as an oxygen scavenger in boiler water, and as an intermediate in the synthesis of numerous agricultural, industrial, and pharmaceutical chemicals. It is estimated that 90,000 workers are potentially exposed to hydrazine (Hz) or its salts each year (NIOSH, 1978). Hydrazine has been employed for many years as a propellant. It was originally used as a jet fuel and a torpedo propellant during World War II in Germany and more recently has been used in Titan II missiles and in the emergency propulsion units of the F-16. The possibility that AF aircraft maintenance personnel may be subject to accidental skin Hz exposure is very real.

Some data are available regarding skin exposure to Hz. The dermal LD_{50} for the rabbit is 91 mg/kg, as compared to an iv LD_{50} of 20 mg/kg (Rothberg and Cope, 1955). The percutaneous absorption of Hz was described by Smith and Clark (1972), who applied Hz to the skin of anesthetized dogs at doses of 3-15 mmole/kg. A chemical burn occurred at the site of application, and absorption appears to have been completed by 70 minutes in all dose groups and sooner in the lower dose groups. The high dose group (15mmole/kg) had a peak serum concentration of 60 μg/ml while the low dose group had a maximum serum concentration of 2 μg/ml. The dermal LD_{LO} for the dog was established as 90 mg/kg.

An azeotropic mixture of 70% Hz and 30% H_2O (H-70) is now used in the emergency propulsion units of the F-16. No data regarding the percutaneous absorption of Hz from H-70 are available. The purpose of this research was threefold; to compare the dermal absorption of Hz from anhydrous Hz and from H-70; to develop data and techniques capable of predicting the rate and extent of Hz and H-70 absorption following skin exposure; and to obtain Hz absorption data from a second species, the rabbit.

MATERIAL AND METHODS

IN VITRO ANHYDROUS Hz AND H-70 EVAPORATION

Fourteen µl of anhydrous Hz, 20 µl of H-70 (the proportionate volumes of Hz and H-70 applied to the rabbits) and 15 µl of H_2O were applied to fiberglass screen covered glass slides. The slides were maintained in a hood at room temperature (22°C) and weighed at intervals to determine the rate of fluid loss via evaporation. The percent loss versus time was plotted for both Hz and H-70.

RABBIT EXPOSURE

Three groups of albino rabbits (Willoughbys Rabbitry, Sabina, Ohio) were treated with Hz. The first group was given anhydrous Hz (>95%, Eastman, Rochester, NY) percutaneously, the second group received H-70 (70% anhydrous Hz, 30% distilled H_2O by volume) percutaneously, and the third group was given Hz intravenously. Each group consisted of five rabbits and all rabbits received a dose of 12 mg of Hz/kg.

The rabbits were anesthetized with a Ketamine (40 mg/kg) and Xylazine (3 mg/kg) mixture given intramuscularly 24 hours prior to Hz application. An iv catheter was placed in the left femoral vein and flushed with heparin solution. Hair was removed from the left lateral thoraco-abdominal region of the rabbit over an 8 cm X 8 cm area. The animals were allowed to recover and held without food overnight. The following morning the rabbits were removed from the cages. To assure even distribution of the fluid on the skin, fiberglass screens were secured on the area intended for application. The rabbits were weighed just prior to Hz or H-70 application. The Hz and H-70 were measured to the nearest µl, placed on the screen covered skin, and spread evenly. A protective stainless steel screen was placed above the skin area exposed to Hz or H-70 and left for the duration of the experiment. Rabbits of the third group were given an iv bolus of 10% Hz in normal saline.

Following the Hz application serial blood samples were taken from the femoral vein of the rabbits. Serum Hz concentrations were determined as described by Reynolds and Thomas (1964).[1]

The group mean serum Hz concentration was determined for each time period and both serum Hz versus time and log serum Hz versus time were graphed. Lines were drawn by inspection or least squares analysis when possible. The Student - t test was used to determine significant differences between the mean serum Hz concentration of the H-70 group and the anhydrous Hz group. The present dose absorbed from anhydrous Hz or H-70 was determined by the equation % dose = (AUC) percutaneous/(AUC) iv where (AUC) is the area under the serum concentration time curve. The (AUC) was determined gravimetrically.

The elimination rate constant for Hz (k_e) is equal to the slope of the semi-logarithmic iv elimination curve and has units of reciprocal time. The half-time ($t_{\frac{1}{2}}$) for Hz elimination was determined from the intravenous group data using the equation $t_{\frac{1}{2}} = 0.693/k_e$. The apparent volume of distribution (Vd) was determined by using the equation Vd(B) = Dose/B, where B is the zero time intercept of the exponential phase of the decline in serum Hz after intravenous administration of a single dose. The Vd gives an indication of the extent of distribution, or tissue binding or both, but provides no information about retention of Hz in specific tissue compartments (Baggot, 1977).

The absorption half-time and absorption rate constant (k_a) were estimated by two methods. A rapid, graphic feathering technique (Figure 1,

[1]We found that monacetylhydrazine and some substituted hydrazones give a similar color reaction to that of hydrazine when reacted with DMBA. However, since the absorbed doses in this study are similar, and the elimination of DMBA color reactants appears to be a first order process, this was not considered a significant problem.

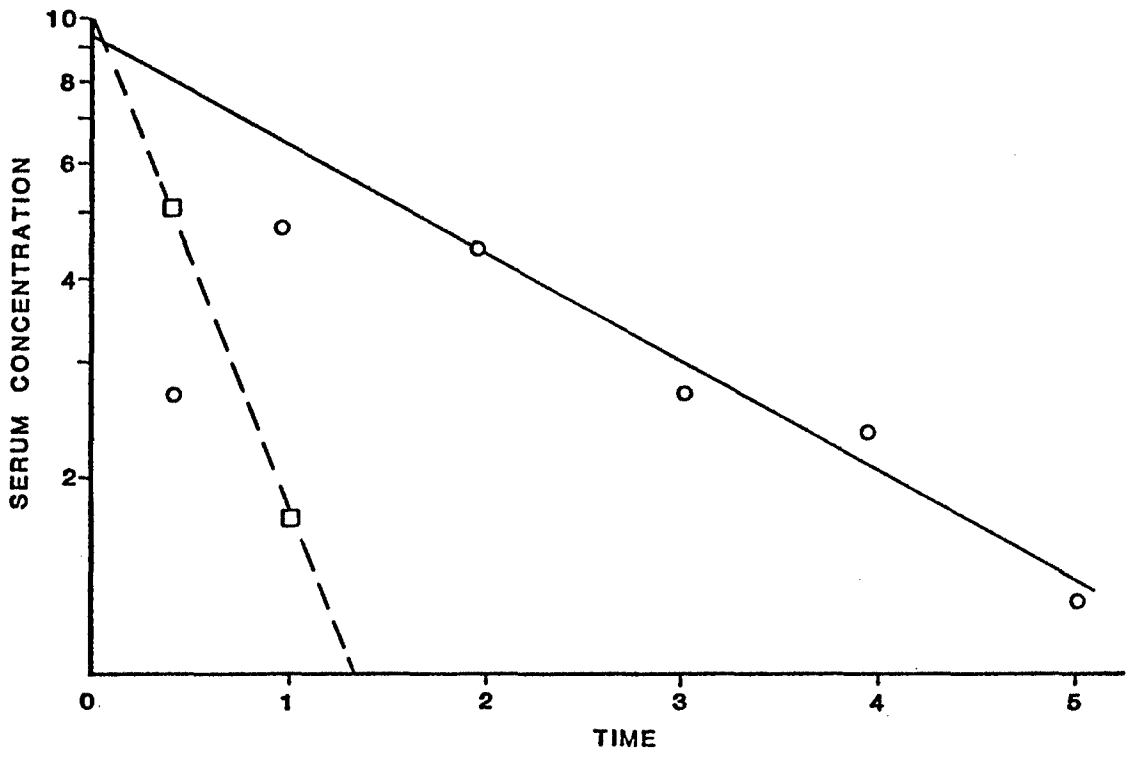

Figure 1

Feathering of Serum Concentration-Time Data

[1] Feathering is accomplished by fitting a line through the terminal portion of the semilogarithmic plot of the serum Hz time data points (thus giving maximum weight to the elimination phase of the curve). This line is extrapolated to time zero and each experimental absorption phase data point is subtracted from it. The value for Ka is estimated from the dashed line which is a semilogarithmic plot of the difference between the experimental values and the extrapolated values (from the solid extrapolated line). This feathering allows the curve to be graphically separated into its two components parts: an elimination (solid line) and an absorption (dashed line) phase.

Notari, 1975) was used and the Wagner and Nelson (1963) equation was also used ($(A/Vd)_{tn} = S_{tn}+K_e \int_{t_o}^{t_n} Sdt.$). In this equation $(A/Vd)t_n$ is the total amount of Hz absorbed at time t_n and $\int_{t_o}^{t_n} Sdt$ is the area under the serum concentration time curve (AUC) from time zero to time t_n. The parameters described previously—Vd(B), $t_{\frac{1}{2}}$, and $(A/Vd)t_n$—are restricted to use on chemicals whose kinetic profiles are adequately described by a one compartment model: that is $S = Be^{-k_e t}$, where S is serum concentration, and B is the zero time intercept of the exponential phase of the decline in serum level after iv administration of a single dose, e is the base of natural logarithms, k_e is the elimination rate constant, and t is the time interval. In this model only the elimination phase is analyzed since rapid distribution precludes measurement of a distributive phase. (For this description the body is conceptually treated as a single homogenous distribution compartment (Notari, 1975 and Baggot, 1977).

RESULTS

ANHYDROUS Hz AND H-70 EVAPORATION

The evaporation profiles of anhydrous Hz and H-70 were identical (figure 2). The rate of fluid loss appears to be biphasic with an initial fast phase followed by a slower phase. About one half the fluid evaporated within 15 minutes. The rate of evaporation of either Hz or H-70 was slower than the rate of H_2O evaporation.

PERCUTANEOUS TREATMENT OF RABBITS WITH Hz

The mean peak serum Hz concentration for anhydrous Hz treated rabbits was 11.1 μg/ml and for the H-70 exposed rabbits was 9.3 μg/ml (Figure 3). Both peaks occurred at 50 to 60 minutes. The percent dose absorbed from the Hz applied to the skin was 86%, while the H-70 hydrazine was absorbed to the extent of only 55%. There was a significant difference (≤ 0.10) in the mean serum Hz concentrations between the anhydrous Hz and H-70 groups at all sample times

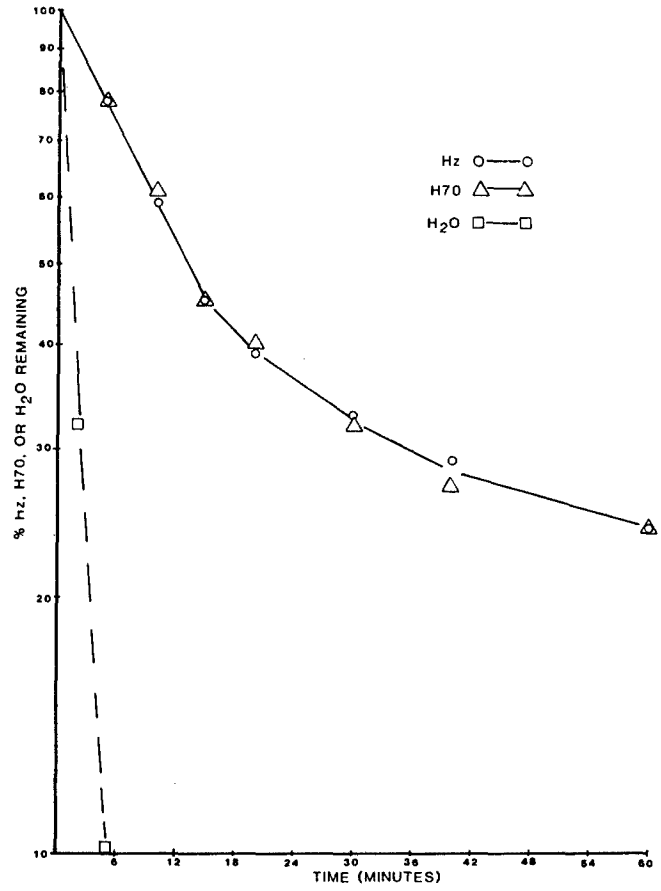

Figure 2. Evaporation of Anhydrous Hz, H-70, or H_2O from a Glass Surface at 22° C

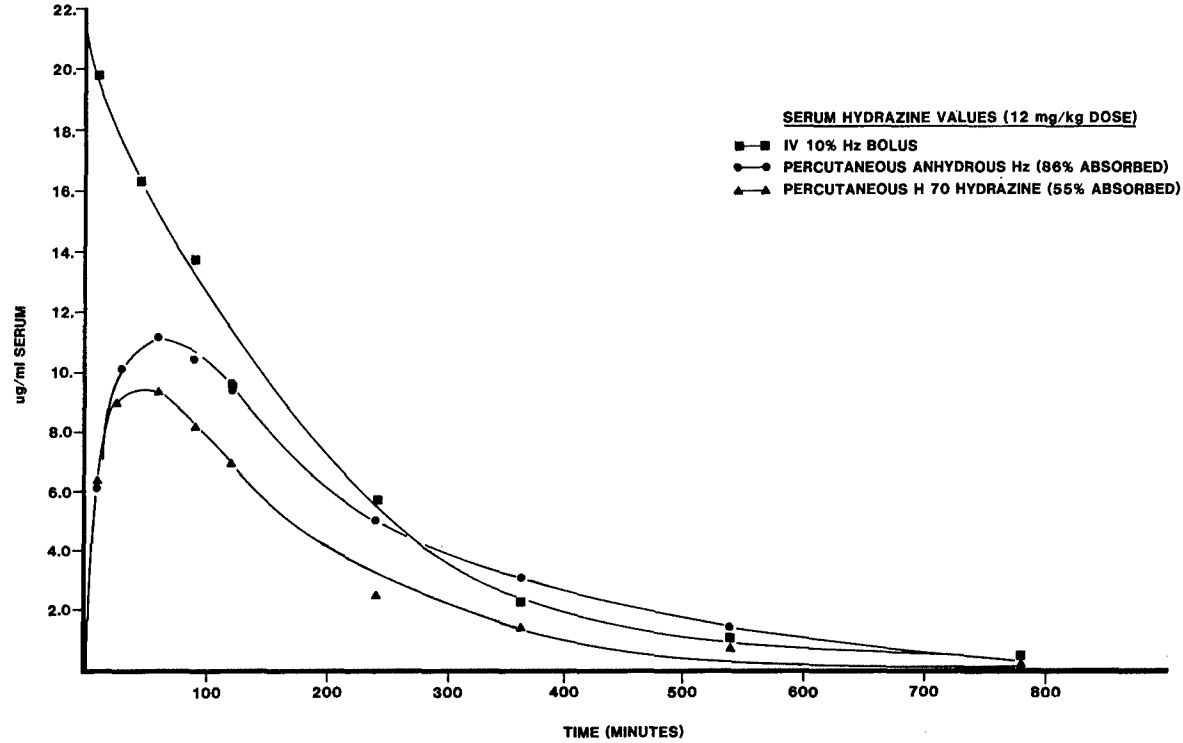

Figure 3. Percutaneous Hz Absorption and Elimination

from one to nine hours. Examination of a semilogarithmic plot of the iv serum Hz time data points clearly shows the absence of a measurable distribution phase (figure 4) which supports the use of a one compartment model. The k_e (slope) was found to be 0.29 hr^{-1}. The serum half-life for Hz was 2.3 hours and the apparent volume of distribution was 0.63 liter/kg. Peak serum Hz concentration was 21 μg/ml for the iv group. The iv dosed rabbits exhibited moderate depression for several hours after treatment while the percutaneous groups did not. The absorption half-life for Hz was 15 minutes by the feathering method (figure 5) and 19 minutes by the Wagner-Nelson equation. The absorption $t_{\frac{1}{2}}$ for Hz from H-70 was 12 minutes by the feathering method (figure 6) and 9 minutes by using the Wagner-Nelson equation. A chemical burn developed following both anhydrous Hz and H-70 applications. The severity, as judged by the darkness of the affected skin, was greater in the anhydrous Hz burns than in the H-70 burns.

DISCUSSION

Both anhydrous Hz and H-70 are well absorbed percutaneously. The observed extent of absorption - 86% and 55%, respectively - is expected with oral, subcutaneous, or intramuscular routes of administration but is relatively uncommon for the percutaneous route. Simple alkylamines (RNH_2) have also been reported to penetrate the skin to a considerable extent (Vinson et al., 1965). The calculated apparent volume of distribution (Vd) for Hz was 0.63 liter/kg which is an intermediate value, as defined by Baggot (1977). While the Vd for Hz is consistent with the distribution of Hz throughout most of the body water (0.60 liter of H_2O/kg), Notari (1975) cautions that Vd is best viewed as a proportionality constant rather than associating it with a particular body H_2O compartment.

Eight-six percent of the anhydrous Hz dose is absorbed when allowed to

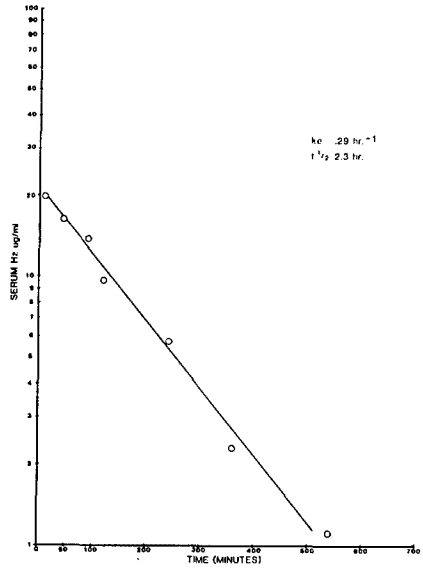

Figure 4. Hz Elimination Following IV Dose

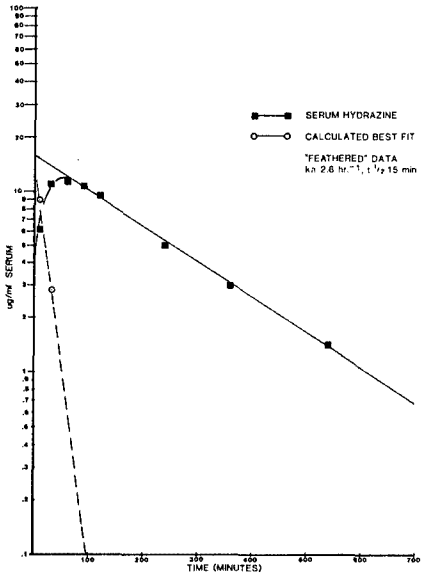

Figure 5. Anhydrous Hydrazine Percutaneous Absorption

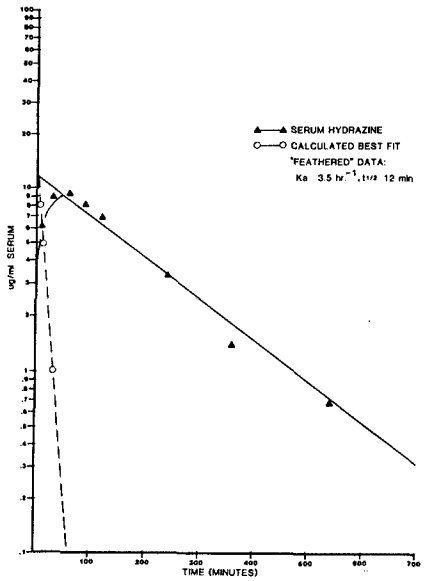

Figure 6. H-70 Hydrazine Percutaneous Absorption

remain on the skin, while only 55% of an equivalent Hz dose is absorbed from a 70% solution (figure 3). The difference in percent dose absorbed cannot be explained by simple evaporation rates since anhydrous Hz and H-70 evaporate at the same rate from the surface of a glass cover slip at 25°c (figure 2). The rate of Hz or H-70 evaporation is relatively slow compared with similar volumes of H_2O which completely evaporated in less than 10 minutes. Simple alkylhydrazines also evaporate more rapidly than Hz itself (NIOSH, 1978). The effect of the comparatively slow evaporation of Hz on the toxicity of a mixture of 50% Hz and 50% unsymmetrical dimethylhydrazine (Aerozine-50) was previously noted by Azar et al. (1970) and Little (1960). Because of the difference in vapor pressure between the hydrazines, most of the toxicity from percutaneous exposure to Aerozine-50 was associated with Hz. The comparatively slow evaporation of Hz allows percutaneous absorption to occur to a greater extent than is possible with more volatile methylated derivatives.

The effect of relatively slow evaporation of Hz and H-70 on percutaneous absorption can be better appreciated by quantitatively examining the simultaneous processes of evaporation and percutaneous absorption as depicted in (figure 7). Notari (1975) has described a method that can be adapted to predict the dose fractions absorbed or evaporated for simultaneously occurring first order processes.

For competing first order processes the fraction absorbed is $k_a/(k_a+k_{evc})$, where k_{evc} is a composite rate constant representing all processes which compete with the blood compartment for Hz. Since the fraction absorbed and k_a are known for both Hz and H-70, k_{evc} can be readily estimated.[2] For absorption of

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[2] $k_{evc} = (k_a D_o/A_\infty)-(k_a)$

$\ln(A_\infty-A_t) - \ln A_\infty - (k_{evc}+k_a)t$

A_t = % dose absorbed at t

A_∞ =% dose absorbed at $t\infty$
k_{evc}=calculated evaporation constant
k_a=absorption rate constant
D_o=dose applied to skin

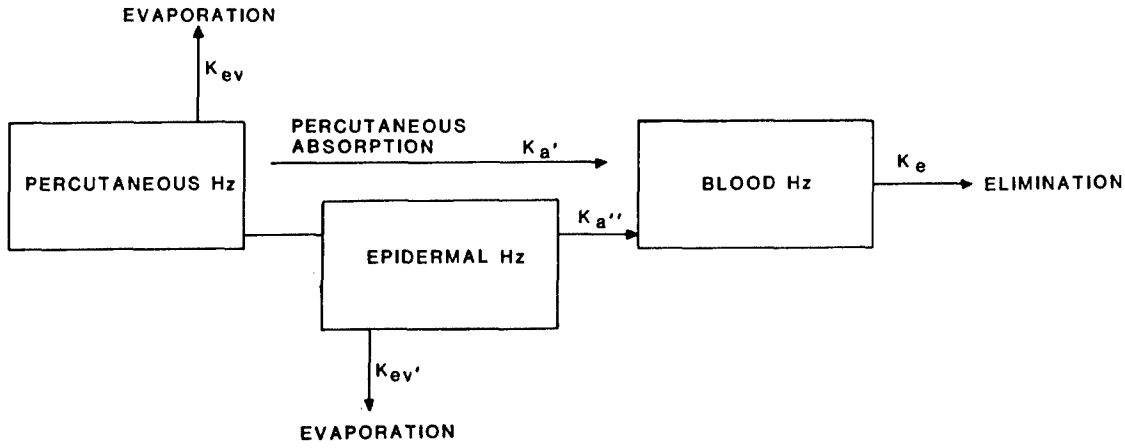

Figure 7. Compartmental Model of Percutaneous Toxicokinetics of Hz [1,2]

1. The absorption constant Ka observed experimentally is a composite of $K_{a'}$ and $K_{a''}$ shown in the kinetic model.

2. The evaporation constant K_{evc} determined by the equation $K_{evc}=(^{KaDo}/_{A\infty})-(Ka)$ is a composite of simple evaporation K_{ev}, evaporation from the epidermal compartment $K_{ev'}$, and Hz lost to epidermal tissue binding and other interactions.

Hz from the H-70, k_{evc} is 3.1 hr^{-1}. The rate constant for the rapid phase of evaporation in vitro was 3.2 hr^{-1} for both anhydrous Hz and H-70. With H-70 the percutaneous absorption is adequately represented by a model in which simple evaporation competes with absorption. (This is true since k_{ev} and k_{evc} are very similar.) With anhydrous Hz, k_{evc} is 0.41 hr^{-1}, substantially lower than k_{ev}. Since the absorption rate constant of anhydrous Hz is not drastically different from that of H-70, the anhydrous Hz could not have been available on the surface for evaporation during the period of absorption. This follows since a composite rate constant can never be smaller than any individual rate constant contributing to it. Kinetic analysis of H-70 and anhydrous Hz absorption shows an apparent retardation of evaporation of anhydrous Hz from the skin surface in vivo. In this case, at least, simple physical determination of evaporation rate constants does not accurately reflect the more complex in vivo behavior on the reactive physiological surface.

A possible reason for this is the more hygroscopic nature of anhydrous Hz as compared to H-70. Since k_a is a rate constant for entry into the blood, not into the skin, anhydrous Hz may be interacting with the skin to form an intermediate Hz compartment, and delaying the movement of Hz into the blood (figure 7). This interaction of Hz with skin may be viewed as local damage that interferes with circulation and slows Hz absorption. This could allow a larger dose fraction to be absorbed over a longer period of time due to the damaged stratum corneum. Alternatively, the interaction may be reversible tissue binding not related to a decrease in circulation to the burn area. The actual process may be a combination of the two factors.

H-70, on the other hand, is an azeotropic mixture of H_2O and Hz, and should not interact with skin as vigorously as anhydrous Hz. One would predict

a lower apparent k_a for anhydrous Hz compared to H-70 Hz, but might also observe a larger absorbed dose fraction. The greater apparent damage to skin by anhydrous Hz compared with H-70 seems to bear this out. In addition, the existence of an epidermal compartment has been previously demonstrated for other chemicals. Kolb et al. (1967) found 20% of a dose of DMSO remaining in the epidermis after 8 hours. The actual rate of Hz penetration of the stratum corneum may by faster for anhydrous Hz than the apparent k_a indicates. This does not seem to be the case with H-70.

The k_a's used to determine the dose fractions absorbed and the k_{evc}'s are averages derived from the $t_{\frac{1}{2}}$'s obtained from each of the two methods for determining absorption rate constants (feathering and Wagner-Nelson equation)[3]. The mean k_a was 3.8 hr^{-1} for H-70 and 2.5 hr^{-1} for anhydrous Hz. The percent dose absorbed at 5 minutes for Hz was estimated as 18% and for H-70 was 24%. These equations show that removal of percutaneous Hz within the first 5 minutes following exposure would prevent >75% of a dose of Hz from either H-70 or anhydrous Hz from being absorbed by the rabbit.

The extent of anhydrous Hz absorption in the rabbit appears to be greater than in the dog. Inspection of the data for dogs (Smith and Clark, 1972) shows that while Hz blood levels peak at about one hour in both dogs and rabbits, the

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[3]The absorption half-time for anhydrous Hz and H-70 Hz as determined by the two different methods were not in complete agreement. The Nelson-Wagner equation derived $t_{\frac{1}{2}}$'s (H-70: 9 min, Hz 19 min) indicate a greater difference in rates of absorption than do the $t_{\frac{1}{2}}$'s derived from feathering (H-70: 12 min., Hz 15 min.) the data (figures 3 and 4). However, both these methods assume a first order absorption process which may not be true. Two other factors which may also compromise the accuracy of these absorption rates should be noted: 1) there are only two data points on the absorption part of the serum Hz versus time curves and 2) the k_a's and k_e for both H-70 and anhydrous Hz are on the borderline for applicability of the feathering technique ($2 < k_a/k_e < 10$). The mean $t_{\frac{1}{2}}$ for anhydrous Hz was 17 min. and for H-70 was 11 min. The mean k_a's were determined by:

$$k_a = 0.693/(t_{\frac{1}{2}}\ \text{Nelson-Wagner} + t_{\frac{1}{2}}\ \text{feathering})/2$$

percutaneous dose necessary to produce serum levels of 10 μg/ml in the dog is greater than 120 mg/kg while in the rabbit it is only 12 mg/kg. These results agree with the literature concerning species differences in skin permeability which clearly shows that percutaneous penetration is more rapid in the rabbit than in the dog (Baggot, 1977). However, there is considerable risk associated with premature comparison of percutaneous absorption between the two species in the absence of iv data in the dog. Comparison of peak serum levels alone ignores the possibility that different Hz elimination rates in the two species are responsible for peak serum Hz differences.

INTERSPECIES EXTRAPOLATION

One cannot reach reliable, quantitative conclusions regarding the hazards of percutaneous human Hz exposure based on results from only two species of experimental animals. Interspecies extrapolation based solely on compartmental models would require percutaneous absorption studies in a variety of experimental animal species. Nevertheless, several qualitative conclusions can be made regarding the potential hazards of acute percutaneous Hz or H-70 exposure in man. First, Hz in H-70 is absorbed to a lesser extent than anhydrous Hz. Second, compared to other major routes of exposure encountered in the occupational environment (i.e. inhalation), percutaneous absorption is relatively slow. Peak Hz blood levels in rabbits after percutaneous Hz application, for example, were much lower than after iv injection (figure 3). In general, acute systemic toxicity correlates more closely with peak blood levels than with total amount absorbed. Third and last, Hz contact with the skin is not a benign event. The chemical is a potent irritant and rapidly produces a severe chemical burn in both dogs and rabbits. Human skin contact with concentrated Hz solutions will be uncomfortable and workers will be likely to wash soon after exposure, thereby limiting the amount absorbed. It is un-

likely that personnel who are aware of the toxic nature of Hz will develop systemic Hz toxicity from percutaneous exposure if they are taking adequate precautions to minimize skin contact and understand the value of rapid water rinse of the exposed area. Percutaneous contact of large portions of the body surface - whole limb immersion, for example — or more limited contact in an incapacitated individual could still have fatal consequences.

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